Original article

Intelligence of very preterm or very low birthweight infants in young adulthood

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ABSTRACT

Objective: To examine the effect of intrauterine and neonatal growth, prematurity and personal and environmental risk factors on intelligence in adulthood in survivors of the early neonatal intensive care era.

Methods: A large geographically based cohort comprised 94% of all babies born alive in the Netherlands in 1983 with a gestational age below 32 weeks and/or a birth weight >1500 g (POPS study). Intelligence was assessed in 596 participants at 19 years of age. Intrauterine and neonatal growth were assessed at birth and 3 months of corrected age. Environmental and personal risk factors were maternal age, education of the parent, sex and origin.

Results: The mean (SD) IQ of the cohort was 97.8 (15.6). In multiple regression analysis, participants with highly educated parents had a 14.2-point higher IQ than those with less well-educated parents. A 1 SD increase in birth weight was associated with a 2.6-point higher IQ, and a 1-week increase in gestational age was associated with a 1.3-point higher IQ. Participants born to young mothers (<25 years) had a 2.7-point lower IQ, and men had a 2.1-point higher IQ than women. The effect on intelligence after early (symmetric) intrauterine growth retardation was more pronounced than after later (asymmetric) intrauterine or neonatal growth retardation. These differences in mean IQ remained when participants with overt handicaps were excluded.

Conclusions: Prematurity as well as the timing of growth retardation are important for later intelligence. Parental education, however, best predicted later intelligence in very preterm or very low birthweight infants.

What is already known on this topic

- Very preterm and very low birthweight infants are at risk of cognitive deficits at school age.
- Disability and functioning has been recently defined by the World Health Organization as a dynamic interaction between neonatal, personal and environmental factors.
- In very preterm and very low birthweight infants, the relative contributions of these factors to cognitive function in adulthood have not yet been described.

What this study adds

- Prematurity as well as the timing of growth retardation are important for later intelligence.
- Parental education, however, best predicts later intelligence in very preterm or very low birthweight infants.

Very preterm and very low birthweight survivors are at risk of later handicap.[1] Even those without obvious handicaps may have cognitive problems affecting educational achievement and professional attainment in adulthood.[2–4]

Gestational age at birth is related to cognitive test scores at school age.[5 6] The immature brain is vulnerable to neonatal complications, such as germinal matrix and intraventricular haemorrhage and periventricular leucomalacia, as well as more subtle abnormalities, such as delayed myelination[7] and reduced brain volume in specific cortical areas.[8] These may affect later cognitive function.

Intrauterine growth retardation (IUGR) is known to have negative consequences for academic achievement and professional attainment in term born infants.[9] Less is known about the effect of IUGR on cognitive outcome in preterm infants. In one study, IUGR in preterm infants was related to early developmental delay and language problems,[10]

and in another to more need of special education than in infants of appropriate size for gestational age (AGA).[11] Weight and head circumference at birth may provide clues to the stage of fetal development at which the growth retardation occurred. Symmetric IUGR, which refers to equally poor weight and head growth, points at a process occurring early to mid pregnancy. Asymmetric IUGR, with relative head sparing, is indicative of growth retardation taking place later in pregnancy. Birth weight irrespective of head circumference predicted learning difficulties in a study of term born children.[12] However, it was intrauterine head growth—and not body growth—that was the major determinant of later intelligence in preterm children.[13 14] Effects of IUGR may thus differ between term and preterm born children. In addition, during neonatal intensive care, preterm children may experience neonatal growth restraint (NGR) and subsequently display a growth pattern similar to children with IUGR.[15] Postnatal rather than intrauterine growth is important for early neurodevelopmental outcome.[16] The effect of NGR on later intelligence, however, is unknown.

According to the classification proposed by the World Health Organization,[17] later functioning and disability are the result of a dynamic interaction between health, personal and environmental factors.

In term born infants, environmental and personal factors such as social class at birth explain more of the variation in later cognitive function than intrauterine growth[18][19] and are important for early development in preterm infants.[20][21] The relative contributions of these risk factors on intelligence in adulthood in survivors of the early neonatal intensive care era have not yet been described.

We report a study in the Collaborative Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS), an ongoing nation-wide follow-up study on the effects of prematurity and dysmaturity on later outcome. In this large geographically based cohort, we examined the effect of neonatal conditions, such as gestational age, intrauterine and neonatal growth, as well as environmental and personal factors, such as maternal age, parental education, sex and origin, on intelligence in adulthood.

SUBJECTS AND METHODS

Subjects

The POPS cohort comprised 94% (n = 1338) of all babies born alive in the Netherlands in 1983 with a gestational age below 32 weeks and/or a birth weight >1500 g.[22] Of the original cohort, 379 did not survive to the age of 19: 312 died in the neonatal period (by definition the first 28 days of life), 51 in the first year of life, and 16 after the first year of life. The remaining 959 were eligible for the present study.

Procedure

Shortly after their 19th birthday, subjects were invited to participate in the study. Participation involved cognitive assessment at one of the 10 participating centres: Emma Children's Hospital AMC, Amsterdam; University Medical Center, Beatrix Children's Hospital, Groningen; University Hospital Maastricht; University Medical Center St Radboud, Nijmegen Leiden; University Medical Center, Leiden; Erasmus MC–Sophia Children's Hospital, University Medical Center Rotterdam; VU University Medical Center, Amsterdam; Wilhelmina Children's Hospital, UMC; Utrecht Máxima Medical Center, Veldhoven; Isala Clinics, Zwolle). Assessments were carried out by trained nurses; details, logistics and response rate have been reported previously.[23] The respective medical ethics review boards of the 10 participating medical centres all approved the study protocol. All subjects provided written informed consent to participate in the study before assessment started.

Outcome

Intelligence was assessed with the computer version of the Multicultural Capacity Test–Intermediate Level developed by Bleichrodt.[24] This recently standardised intelligence test differentiates within the lower half of the IQ spectrum and measures capacity and skills of individuals with secondary education. It derives an IQ with a mean of 100 and a standard deviation of 15 in the Dutch norm sample.

Risk factors

Environmental and personal risk factors were: maternal age (in tertiles); highest education of the parents (low, primary school or junior secondary vocational education; intermediate, general or senior secondary education; high, higher vocational education or university); sex; origin (Caucasian, non-Caucasian). Neonatal factors were gestational age (in weeks) and weight (in g), length (in cm) and head circumference at birth (in cm) and 3 months of corrected age. Weight, length and head circumference were expressed as standard deviation scores (SDS) to adjust for (gestational) age and sex.[25][26] Subjects with a birth weight and/or length $<-2\text{SD}$ were labelled IUGR. Symmetric IUGR was defined as both birth size and head circumference $\leqslant -2$ SD below the mean for the infant's gestational age. Asymmetric IUGR was defined as birth size $\leqslant -2$ SD and head circumference $>-2\text{SD}$. Those with weight and length above -2SD at birth as well as at 3 months were labelled AGA. Infants with weight and length above -2SD at birth and with weight and/or length $<-2\text{SD}$ at 3 months were labelled AGA-NGR.[15]

Statistical analysis

Multiple imputation was applied to adjust for missing values (correcting for positive selection bias).[23][27] This simulation-based approach creates a number of imputed (completed) datasets by "filling in" plausible values for the missing data. The imputations are based on a model that uses information from other variables to achieve optimal estimates. Only imputations for the missing values between the lowest and highest values of the measured outcome variable are valid. Uncertainty about the model estimates is reflected in differences between imputations in the different completed datasets. Realistic complete data estimates can be attained by pooling results from the completed datasets. We used the MICE (multivariate imputation by chained equations) software program[28] to create five imputed datasets, based on the neonatal, environmental and personal factors mentioned above and all available outcome-specific data at ages 5, 10, 14 and 19 years of age. We applied predictive mean matching to create multiple imputations. Confidence intervals for the outcomes were estimated by pooling the multiple imputations.[29]

Group differences for categorical variables were analysed by analysis of variance. Multiple regression analyses were performed to analyse the importance of the factors simultaneously. We assessed whether environmental and personal factors, the severity and timing of growth retardation (expressed as birth weight SDS and asymmetric IUGR, symmetric IUGR or AGA-NGR) and gestational age were risk factors for intelligence at 19 years of age. Analyses were performed firstly with physical and cognitive handicaps included, and secondly with handicaps excluded. The unstandardised regression coefficient (symbolised by B), including 95% CI, and the standardised regression coefficient (β) are presented. Data were analysed with the SPSS V12.1 software program.

RESULTS

Of the survivors, 12.6% was handicapped and had moderate to severe problems in cognitive or neurosensory functioning,[27] 596 of the 959 (62.1%) participated in the assessments,[23] and 562 (94.3%) completed the intelligence test (IQ) at a mean (SD) age of 19.3 (0.2) years.

Table 1 shows the characteristics of the study group in relation to IQ. The following values are expressed as mean (SD). IQ at 19 years of age was 97.8 (15.6) (95% CI 96.5 to 99.1); 4.3% had an IQ<70. Maternal age at birth was 27 (4.8) years, and gestational age was 31 (2.5) weeks. At birth, mean weight was 1314 (283) g, weight SDS was −0.9 (1.6), mean length SDS was −0.8 (1.6), and mean head circumference SDS was −0.6 (1.4). At 3 months of age, mean weight SDS was −1.3 (1.5), and mean length −1.3 (.4). Maternal age at birth was missing in 12, parental education in 18, origin in six, gestational age in one, length and head circumference at birth in 134 and 80, respectively, and weight, length and head circumference at

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Table 1 Characteristics of the study group before and after multiple imputation (MI) in relation to IQ at age 19

Characteristic	Before MI No	%	After MI (%)	IQ Mean (SD)	95% CI
Environmental and personal factors					
Maternal age at birth (years)					
<25	174	31.6	34.9	94.9 (15.0)	94.2 to 95.7
25–30	214	38.9	38.0	99.5 (16.0)	99.1 to 99.9
>30	162	29.5	27.1	99.2 (15.3)	98.7 to 99.6
Parental education					
Low	172	32.0	38.9	92.2 (14.3)	91.2 to 93.2
Intermediate	208	38.2	36.2	98.6 (15.0)	98.2 to 99.0
High	162	29.8	24.9	106.2 (14.7)	105.7 to 106.7
Sex					
Male	255	45.4	51.8	98.8 (16.6)	98.5 to 99.2
Female	307	54.6	48.2	96.7 (14.4)	96.4 to 97.1
Origin					
Caucasian	496	89.2	85.3	98.1 (15.6)	97.8 to 98.3
Non-Caucasian	60	10.8	14.7	96.5 (15.2)	95.8 to 97.1
Neonatal factors					
Gestational age (weeks)					
<32	413	73.6	70.5	98.4 (15.9)	98.1 to 98.7
≥32	148	28.4	29.5	96.4 (14.9)	96.0 to 96.9
Growth					
AGA	274	56.5	53.7	99.7 (15.7)	98.7 to 100.7
AGA-NGR	79	16.3	17.3	95.5 (15.8)	93.6 to 97.4
Asymmetric IUGR	46	9.5	12.1	97.4 (14.6)	96.7 to 98.1
Symmetric IUGR	86	17.2	16.9	94.6 (14.9)	94.0 to 95.2

AGA, appropriate size for gestational age; IUGR, intrauterine growth retardation; AGA-NGR, neonatal growth restraint.

3 months of age in 48, 73 and 85 of the 562 participants, respectively. Because of colinearity, stepwise multiple regression analyses were performed for birth weight and gestational age (fig 1) and for asymmetric and symmetric IUGR and AGA-NGR (table 2) separately.

Figure 1 presents differences in mean IQ for gestational age and birth weight SDS, environmental and personal factors in multiple regression analyses. A high parental education was the
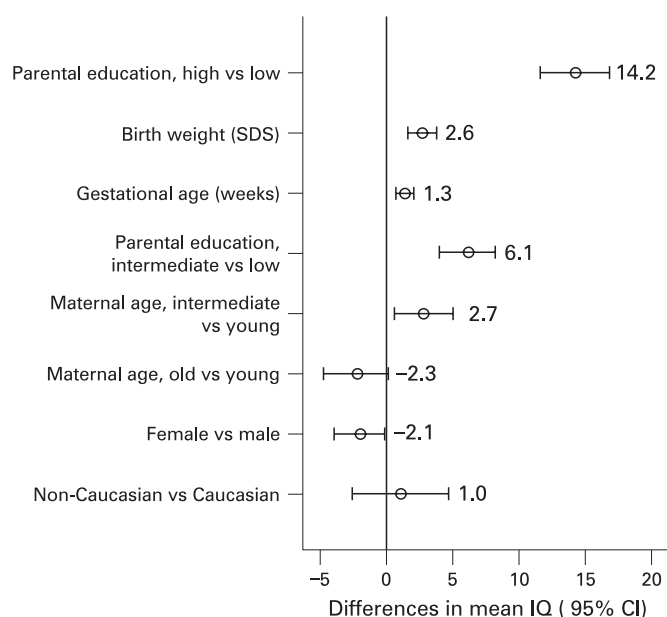

Figure 1 Differences in mean IQ for gestational age and birth weight SDS and environmental and personal factors in multiple regression analyses.

best predictor of IQ at 19 years of age (β 0.39), followed by birth weight SDS (β 0.27), gestational age (β 0.22), maternal age at birth >25 years (β 0.08 and 0.07) and sex (β 0.07). Participants with highly educated parents had a 14.2-point higher IQ than those with less well-educated parents. A 1 SD increase in birth weight was associated with a 2.6-point higher IQ, and a 1-week increase in gestational age with a 1.3-point higher IQ. People with mothers aged 25–30 years at birth had a higher IQ than those with younger mothers (mean difference 2.7 points). Men had a higher IQ than women (mean difference 2.1 points). Comparable results were obtained when multiple regression analyses were repeated with handicaps excluded.

Table 2 presents differences in mean IQ for different growth conditions corrected for environmental and personal factors in multiple regression analyses. With handicaps included, subjects born after symmetric IUGR lost 5.8 IQ points (β 0.14), those born after asymmetric IUGR lost 3.7 IQ points (β 0.08), and those with NGR lost 4.1 IQ points (β 0.10). With handicaps excluded, these losses were 5.3, 3.6 and 3.2 IQ points, (β 0.13, β 0.08, β 0.08), respectively.

DISCUSSION

In our cohort, the mean IQ was 97.8 (15.6) on a very recently standardised test. This good outcome at young adulthood in these survivors from the early neonatal intensive care era is in agreement with the recent Canadian study of Saigal et al[4] and may largely be attributable to the favourable socioeconomic circumstances. All families had access to healthcare and could benefit from the Dutch social service system, 85% were of Caucasian origin, and parental education was high in 25%. Parental education best predicted later intelligence. After adjustment for the influence of all other variables, participants with highly educated parents scored almost 1 SD in mean IQ

Table 2 Differences in mean IQ for different growth conditions

| Characteristic | IQ | | | |
| | Handicaps included | | Handicaps excluded | |
	B (95% CI)	β	B (95% CI)	β
Gestational age (weeks)	0.5 (−0.1 to 1.0)	0.07	0.4 (−0.1 to 0.9)	0.07
Growth				
AGA	–	–	–	–
AGA-NGR	−4.1 (−6.6 to −1.5)	−0.10	−3.2 (−6.3 to −0.1)	−0.08
Asymmetric IUGR	−3.7 (−7.1 to −0.4)	−0.08	−3.6 (−6.7 to −0.6)	−0.08
Symmetric IUGR	−5.8 (−9.1 to −2.5)	−0.14	−5.3 (−8.5 to −2.1)	−0.13

The unstandardised regression coefficient (B), 95% CI and the standardised regression coefficient (β) of the neonatal factors, adjusted for influence of environmental and personal factors in the model (eg, maternal age at birth, parental education, sex and origin).
AGA, appropriate size for gestational age; IUGR, intrauterine growth retardation; AGA-NGR, neonatal growth restraint.

points higher than those with less well-educated parents, probably reflecting genetic as well as educational influences. People whose mothers were aged 25–30 years when they were born had a higher IQ than those born to younger or older mothers. This U-shaped effect of maternal age on intelligence is in line with findings from other developmental studies in non-premature populations.[30] Maternal age reflects both socio-economic and personal age-related factors such as experience and physical endurance. In the POPS study, as in most other follow-up studies, at an early age, the handicap risk was significantly greater for boys than for girls.[31] For intelligence, this male disadvantage had disappeared at 19 years of age. As we performed multiple imputations, this cannot be explained by the fact that the male subjects followed had higher maternal education and socioeconomic level than those lost to follow-up and may be catching up. Genetic conditions may account for up to 72% of the variance in intelligence.[32] In children at high biological risk, however, these genetic factors may be over-shadowed by environmental factors.[33] In these children, an optimal environment can compensate for a cognitive delay.[20 21]

In our study, neonatal factors at first sight had relatively little effect on intelligence compared with parental education. One SD more in birth weight resulted in 2.6 IQ points more, and 1 week in gestational age resulted in 1.3 IQ points more. Compared with subjects born at 36 weeks, however, those born at 26 weeks have on average 13.0 lower IQ points. Our findings in this respect are comparable to those of a meta-analysis of intelligence in school-aged children who were born very preterm, with a 10.9 mean IQ point differences between the very preterm and the controls.[5]

The effect on intelligence in premature infants after early symmetric IUGR was more pronounced than after asymmetric IUGR. Owing to an increased risk of handicap during neonatal intensive care, however, the effect of NGR on intelligence was more serious than that of asymmetric IUGR. In this study, we were unable to differentiate small "normal" children from IUGR children. Moreover neonatal data were collected at a time when cerebral ultrasound was not routinely available. Neonatal complications such as cerebral haemorrhage or periventricular leucomalacia may result in overt handicaps that can be diagnosed at an early age. However, very preterm and very low birthweight infants develop cognitive problems in the absence of overt handicaps or neuroimaging abnormalities.[34 35] To study these more subtle effects, we performed analyses in which participants with overt cognitive or neurosensory handicaps were excluded. The effect of NGR became less pronounced. Yet, the timing of the growth retardation remained a significant predictor of intelligence, suggesting that overt

neonatal cerebral brain damage leading to overt handicaps does not explain these differences in IQ. This study does not have the potential to identify the precise mechanisms underlying these differences in IQ. Neonatal factors contributing to neurobehavioral deficits may include the vulnerability of the immature brain both before and after birth, multiple clinical problems specific to prematurity, stressful environmental conditions, and multiple painful procedures. Moreover, neonatal hospital stay may hamper the quality of infant–parent interaction.[36]

We conclude that neonatal factors such as gestational age at birth and intrauterine and neonatal growth are of predictive value. The effect on intelligence after early (symmetric) IUGR is more pronounced than after later (asymmetric) intrauterine or NGR. Environmental factors, however, especially parental education, best predict later intelligence. In our study, parental education was relatively high. The good outcome at young adulthood in these survivors from the early neonatal intensive care era seems therefore to be partly due to the favourable socioeconomic circumstances of the study group growing up in Dutch society, which is representative of most Western societies. Even very preterm children with normal IQ, however, are at risk of neuropsychological deficits that may result in learning and behavioural problems. In our study compared with the general Dutch population, although the mean IQ in our cohort was only 2.2 IQ points lower, twice as many young adults who had been born very preterm and/or with a very low birth weight were poorly educated (24% vs 12.8%) and three times as many were neither employed nor in school (7.6% vs 2.6%) at 19 years of age.[27] Today we are witnessing an increase in the number of preterm births in many countries in the Western world. Prevention of preterm birth should therefore have high priority. An optimal environment during fetal life as well as during neonatal intensive care is warranted to prevent neonatal complications and growth restraint. After discharge, early intervention programmes should focus on the prevention of neurocognitive deficits and promote the parent–child relationship. In addition, support for children growing up in less favourable socioeconomic circumstances is needed.

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